IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s): Weichao G. Chen et al.

Examiner: Evelyn Huang

Serial No: 09/836,035

Art Unit: 1625

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Docket: PC10866A (16575)

For: SODIUM-HYDROGEN EXCHANGER TYPE 1 INHIBITOR

Dated: March 22, 2004

Confirmation No.: 8768

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

RESPONSE UNDER 37 C.F.R. §1.111

Sir:

This is in response to the outstanding Official Action dated October 20, 2003.

CERTIFICATE OF MAILING UNDER 37 C.F.R. §1.8(a)

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231, on March 22, 2004.

Dated: March 22, 2004

Marvin Bressler

All the claims submitted for examination in this application have been rejected on substantive grounds. Applicants have considered these grounds of rejection and respectfully submit that none of them make unpatentable any of the claims currently in this application.

Five substantive grounds of rejection have been imposed in the outstanding Official Action. The first substantive ground of rejection is directed to Claims 1 to 29 of the present application. Claims 1 to 29 stand rejected, under 35 U.S.C. §102(a), as being anticipated by International Publication No. WO 99/43663 to Hamanaka et al.

The Official Action avers that Hamanaka et al. discloses the prior art compound [(5-cyclopropyl-1-quinolin-5-yl)-1H-pyrazole-4-carbonyl]guanidine. The Official Action avers that that compound would be metabolized to (5-cyclopropyl-1-(2-quinolon-5-yl)-1H-pyrazole-4-carbonyl]guanidine by hydroxylation.

It is axiomatic that an anticipatory reference must disclose each and every limitation of a claim. In the present application the claim is a compound. Applicants respectfully aver that Hamanaka et al. does not disclose each and every limitation of any of Claims 1 to 29.

The Official Action admits that the sole basis for this ground of rejection is the disclosure of the compound of the first of the two compounds recited in Claim 103 of Hamanaka et al. That compound is admitted in the Official Action to be different from the compound (5-cyclopropyl-1-(2-quinolon-5-yl)-1H-pyrazole-4-carbonyl]guanidine, a species within the contemplation of the generic formula of Claim 1 of the present application but specifically excluded therefrom.

The theory advanced in the outstanding Official Action, that there is a so-called "inherent anticipation" of that compound, is predicated upon the fact that a compound within the scope of the present application would be metabolically formed in the body by

hydroxylation. As such, the limitation in Claim 1, wherein the statement is made that the compound of that claim encompasses prodrugs thereof, establishes anticipation. However, the specific exclusion of [5-cyclopropyl-1-(quinolin-5-yl)-1H-pyrazole-4-carbonyl]guanidine eliminates the possibility that any compound within the contemplation of the Hamanaka et al. disclosure is within the scope of Claim 1, from which all the remaining claims ultimately depend.

It is emphasized that applicants do not contest the principle that inherent anticipation does not require that a person of ordinary skill in the art at the relevant time would have recognized the inherency disclosure. The claimed invention may be inherently anticipated even if the prior art supplies no express description of any part of the claimed subject matter, since the prior art reference that expressly or inherently contains each and every limitation of the claims is anticipated by the reference. Schering Corp. v. Geneva Pharmaceuticals Inc., 339 F.3d 1373, 67 USPQ2d 1664 (Fed. Cir. 2003). Rather, applicants submit that there is no inherent anticipation disclosed in the reference.

As indicated in applicants' earlier response, filed on November 16, 2001, the allegation that the compound within the scope of the present application is a metabolite of the compound disclosed in Hamanaka et al., and thus a prodrug thereof, is irrelevant insofar as the prodrug compound relied upon is specifically excluded from the class of compounds within the contemplation of all those claimed in this application. As such, it is apparent that Hamanaka et al. does not infringe any of the claims of the present application.

It is furthermore noted that not only is there nothing in Hamanaka et al. which establishes that the relied upon compound of that reference is a prodrug of a species within the contemplation of the compounds of the present application. In any event the exclusion of

the compound [(5-cyclopropyl-1-quinolin-5-yl)-1H-pyrazole-4-carbonyl]guanidine makes this point moot.

The second substantive ground of rejection is closely related to the first. The second ground of rejection is directed to all the claims currently in this application, Claims 1-29 and 31. These claims stand rejected, under 35 U.S.C. §103(a), as being unpatentable over Hamanaka et al.

The Official Action argues that the specific compound of Claim 103 of Hamanaka et al. differs from the compound of Claim 31 of the present application which, of course, is within the contemplation of the generic class of compounds of Claim 1, insofar as the instant compound includes an additional hydroxy group at the 2-position on the quinolinyl moiety. The hydroxy group tautomerizes to an oxo group. The Official Action argues that since Hamanaka et al. teaches that the hydroxy group is an optional substituent, the compound of Claim 31 is obvious.

Applicants submit that the Official Action allegation that Hamanaka et al. suggests the optional inclusion of hydroxy at the 2-position is incorrect. A clear reading of Claim 102 of Hamanaka et al. indicates that the R^2 bicyclic ring is optionally mono- or di-substituted with hydroxy. This recitation does not indicate that the hydroxy group is on the 2-position. Moreover, as stated above, the R^2 bicyclic ring may not only be optionally mono-substituted but, additionally, may be di-substituted. Thus, the number of compounds within its contemplation is quite large indeed. However, this point is of academic interest insofar as the Official Action admits that the presence of an unexpected result for the species of Claim 31 rebuts any presumption of obviousness.

The Declaration under 37 C.F.R. §1.132, executed by Mary Allen on November 16, 2001, hereinafter the Allen Declaration, rebuts any presumption of obviousness. The Official Action, however, indicates that the Allen Declaration is insufficient to overcome the rejection on two grounds.

The first of these reasons is that the unexpected result, longer plasma half-life, is not described in the specification. Applicants respectfully submit that absence of a disclosure of an unexpected result in a specification has no adverse effect on the adequacy of a showing provided in a Rule 132 declaration.

It is well established that when a specification is silent regarding the advantages or problems solved by a claimed invention, the proffering by an applicant of evidence of unexpected results is persuasive even in the absence of any mention of those advantages in the specification. The Federal Circuit has held that evidence advanced subsequent to the filing of a specification silent regarding that evidence still rebuts any presumption of obviousness in a traverse of a 35 U.S.C. §103 rejection. In re Chu, 66 F.3d 292, 36 USPQ2d 1089 (Fed. Cir. 1995). As such, the first ground advanced for the non-persuasiveness of the proffered Declaration is unsustainable.

The second ground in support of the alleged insufficiency of the earlier submitted Allen Declaration is that the compound of Claim 103 of the applied Hamanaka et al. reference reads on the instant compound recited in Claim 30.

The specific exclusion, in Claim 1, of the compound of Claim 103, when taken with the earlier cancellation of Claim 30 of the present application, removes any claiming of the prior art Hamanaka et al. compound from the scope of the present application. Thus, even if the compound of Hamanaka et al. is metabolized to produce a compound within the

contemplation of the present application, this disclosure is made in the present application, not available as a reference, rather than the applied Hamanaka et al. disclosure. Thus, all Hamanaka et al. teaches is the specifically excluded compound.

The Allen Declaration appropriately rebuts any presumption that the disclosure of [5-cyclopropyl-1-(quinolin-5-yl)-lH-pyrazle-4-carbonyl]guanidine makes obvious the compound (5-cyclopropyl-l-(quinolon-5-yl)-lH-pyrazole-4-carbonyl)guanidine. The showing of the Allen Declaration establishes that, in spite of the structural similarity of the two compounds, the longer plasma half-life of the compound of the present application is more efficacious than the compound disclosed in Hamanaka et al. compound. This is so because the compound of the present application is of longer acting duration, resulting in more flexible dosing, than the prior art Hamanaka et al. compound. As such, it is established that the claimed compound of the present application produces an unexpected result over the prior art Hamanaka et al. compound.

The third substantive ground of rejection is similar to the second ground of rejection. This third rejection, imposed under 35 U.S.C. §103(a), is again directed to Claims 1 to 29 and 31, all the claims of the present application, over Hamanaka et al. taken in view of Principles of Pharmacology, Basic Concepts & Clinical Applications (1995) edited by Munson et al. and Beedham et al., Drug Metabolism and Disposition, 20 (6), 889-895 (November, December, 1992).

The Official Action argues that Munson et al. discloses that hydroxylation reactions are well known in the pharmaceutical arts as a phase I metabolic transformation of drugs. The oxidation of quinoline to 2-quinolone by an oxidase from the liver is described in the

Beedham et al. abstract. Thus, the prior art quinoline compound is a prodrug of the instant quinolone compound and is expected to share similar biological activities.

It is unnecessary to reiterate the earlier submitted arguments which establish that Munson et al. teaches that metabolism may occur under phase I or phase II metabolic transformation and that there are multiple types of phase I transformations. The teaching of Munson et al., as summarized in applicant's earlier response, is that the likelihood of metabolism, the type of metabolism, the extent of metabolism and the position of metabolism in a molecule cannot be predicted without extensive experimentation.

As far as Beedham et al. is concerned, that reference discloses oxidation at the 2-position of a quinoline ring. However, as discussed in applicants' earlier response, the compounds disclosed therein are dissimilar to applicants' claimed compounds. As taught in Munson et al., not only may a wide variety of mechanisms be involved in a metabolic reaction but, in addition, a wide variety of different substrates are vulnerable to transformation. As such, while the instant invention and Beedham et al. share a quinolone moiety in their respective compounds, other groups on the respective compounds may be metabolized instead of or in addition to the group in question to provide very different compounds.

As a result, a person of ordinary skill in the art would not be motivated to combine the Hamanaka et al., Munson et al., and Beckham et al. disclosures. Applicants' earlier response cited a Federal Circuit case, In re Dow Chemical Co. for the well established proposition that the requisite motivation to combine references must come from the prior art, not applicants' specification. Many other such citations, such as In re Rouffet, 149 F.3d 1350, 47 USPQ2d 1453 (Fed. Cir. 1998), can be mentioned in support of this well established proposition. Indeed, the instant ground of rejection is nothing more than the utilization of the present

specification as a template to guide the citation of the references applied in the present ground of rejection.

The above remarks are directed to the absence of any prima facie case of obviousness presented by the three applied references. However, this is superfluous in view of the showing of unexpected results, presented in the Allen Declaration, which rebuts any presumption of obviousness created by the combined teaching of the three references. The superior properties of the compound of the present application establishes patentability, under 35 U.S.C. §103(a), over the three applied references independent of whether the three references present a prima facie case of obviousness, which, as stated above, is not presented in the instant ground of rejection.

The fourth substantive ground of rejection is made on identical grounds as the third ground. That is, all the claims of the present application, Claims 1-29 and 31, stand rejected, under 35 U.S.C. §103(a), as being unpatentable over Hamanaka et al. taken in view of Munson et al. and Beedham.

It is unnecessary to respond to this ground of rejection. It is not clearly understood how this ground of rejection, set forth in Paragraph 6 of the outstanding Official Action, differs from the rejection imposed in Paragraph 4 of the outstanding Official Action. Suffice it to say, the above remarks apply to this ground of rejection insofar as the three applied references do not present a prima facie case of obviousness and that, even if they did, which is not the case, the showing of unexpected results presented in the Allen Declaration rebuts that presumption.

The fifth substantive ground of rejection is directed to all the claims currently in this application, Claims 1-29 and 31, under the judicially created doctrine of obviousness-type double patenting over Claims 52 and 124 to 128 of U.S. Patent 6,492,401 to Hamanaka et al.

Suffice it to say, these claims recite the compound [5-cyclopropyl-1-(quinolin-5-yl)-1H-pyrazole-4-carbonyl]guanidine as a compound in Claim 52 and in Claims 124 to 128 refer to a method of reducing tissue damage utilizing that compound.

The above remarks, which establish that this disclosure does not make obvious the claims of the present application, especially in view of the Allen Declaration, which establishes unexpectedly results for the structurally similar but non-identical compound within the scope of the present application, [5-cyclopropyl-1-(quinolon-5-yl)-1H-pyrazole-4-carbonyl]guanidine, are sufficient to establish that the mere disclosure of [5-cyclopropyl-1-(quinolin-5-yl)-lH-pyrazole-4-carbonyl]guanidine in the applied claims is not enough to sustain the obviousness-type double patenting of Claims 1 to 29 and over Claims 52 and 124 to 128 of Hamanaka et al.

The above extensive remarks establish the patentable nature of all the claims currently in this application. Notice of Allowance and passage to issue of these claims, Claims 1-29

and 31 is therefore respectfully solicited.

Respectfully submitted,

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